Full title:

PHARMACOVIGILANCE IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS (PHARMACHILD) TREATED WITH BIOLOGIC AGENTS AND/OR METHOTREXATE.
A PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO)/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY (PRES) REGISTRY

Protocol acronym:
Pharmachild JIA registry

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Participating centres belonging to the Pediatric Rheumatology International Trials Organisation (PRINTO at www.printo.it) or the Pediatric Rheumatology European Society (PRES at www.pres.org.uk)

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ABSTRACT

BACKGROUND: Juvenile idiopathic arthritis (JIA) (1) is the most common chronic paediatric rheumatic disease (PRD) and an important cause of short and long-term disability and quality of life impairment (2-6). Although none of the available drugs for JIA has a curative potential, prognosis has greatly improved as a result of substantial progress in disease management. The therapeutic treatment of children with JIA encompasses the use of non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroid injections. In those patients not responding to NSAIDs, methotrexate (MTX) (7-9) has become the disease modifying anti-rheumatic drug (DMARD) of first choice worldwide. For children not responding to MTX, biologic agents recently have become treatment options (10-15).

PATIENTS AND METHODS: This 3-10 year project will observe children with JIA undergoing treatment with biologic agents±MTX, as the primary disease model and has the following objectives:

1. To create a long-term observational registry of a large population of prevalent and incident cases of JIA treated with biologic agents±MTX with or without concurrent medications.
2. Use the accumulating data in the registry to conduct (i) a pharmacovigilance/safety study (**primary endpoint)** and (ii) estimate effectiveness (frequency and magnitude of response, disease activity over time inhibition or slowing of joint erosions and other radiological evidence of disease progression), and (iii) estimate adherence to the various treatment regimens. Data from the registry will be used to compare safety and effectiveness profiles amongst the patient cohorts.
3. To identify clinical and laboratory predictors of safety, response to therapy, including remission

This project has retrospective (first 3 years) and prospective components (up to 10 years) and will be conducted by the participating centres of the more than 50 countries belonging to the Paediatric Rheumatology INternational Trials Organisation (PRINTO certified ISO 9001-2008, www.printo.it), or the Pediatric Rheumatology European Society (PRES at www.pres.org.uk). The main role of these organisations is to provide a scientific basis for current treatments of paediatric rheumatic diseases.

SIGNIFICANCE AND LONG TERM GOALS: The rationale underpinning this collaborative project is to combine the efforts of paediatric rheumatologists belonging to the PRINTO/PRES network in order to guarantee a critical mass of patients' data, which is essential to answer the questions above, and eventually to fulfil the unmet medical needs in JIA, and to provide systematically obtained evidence for development of guidelines for health authorities.

BACKGROUND

Introduction

Juvenile idiopathic arthritis (JIA) (1) is the most common chronic paediatric rheumatic disease and an important cause of short and long-term disability and quality of life impairment (2-6). Although none of the available drugs for JIA have a curative potential, prognosis has greatly improved as a result of substantial progress in disease management.

Intra-articular steroid injections are indicated in mono or oligoarticular arthritis in association with or in substitution for non steroidal anti-inflammatory drugs (NSAIDs) while in other JIA categories they are usually used in association with systemic treatments.

Undoubtedly, methotrexate (MTX) at a dose of 15 mg/m^2/week administered parenterally is the second line agent of first choice for the treatment of children with polyarticular JIA who do not respond to NSAIDs (7-9;16). About one-third of these patients do not respond or are intolerant to MTX and are therefore candidates for treatment with biologic agents such as etanercept, infliximab, adalimumab, abatacept (10-15) and others currently in development. Other alternatives include cyclosporine (17), leflunomide (18), and sulfasalazine (19). When a biologic agent fails then another biologic agent is usually considered. However, little information exists on the long term safety of these agents that are currently being used in children with JIA. The availability of a large observational registry of subjects with JIA treated with second line agents and biologics will enable clinicians and regulatory agencies to monitor the long-term safety (primary goal of this effort) of these agents. Additionally, accompanying efficacy information will permit the determination of the extent to which these drugs do more good than harm under the usual circumstances of healthcare practice in JIA. Long-term effectiveness data will permit estimation of probability of response over time, and whether these agents inhibit joint erosions and damage.

This 3-10 year project will observe children with JIA undergoing treatment with MTX or biologic agents as the primary disease model and has the following objectives:

1. To conduct a long-term observational pharmacovigilance/safety (**primary endpoint)** and effectiveness (magnitude of response, slowing of joint erosions and other damage, and treatment adherence of various forms of administration) study by creating a registry in a large population of prevalent and incident cases of any JIA categories treated with MTX or biologic agents
2. To identify clinical and laboratory predictors of safety, response to therapy, including remission
3. To establish 3 different cohorts of children (treated with either MTX alone, biologics with or without concomitant MTX, or not treated with MTX or biologics). Each cohort will be used as a comparator for the others.

This project will be conducted by the participating centres of the more than 50 countries belonging to the Paediatric Rheumatology INternational Trials Organisation (PRINTO certified ISO 9001-2008, www.printo.it), or the Pediatric Rheumatology European Society (PRES at www.pres.org.uk). The main role of these organisations is to provide a scientific basis for current treatments of paediatric rheumatic diseases. The rationale underpinning this collaborative project is to combine the efforts of paediatric rheumatologists belonging to the PRINTO/PRES network in order to guarantee a critical mass of patient' data which is essential to answer the unmet medical needs in JIA and to provide systematically obtained evidence for development of guidelines for health authorities.

Brief description of JIA

JIA is a broad term that describes a clinically heterogeneous group of arthritides of unknown cause, which begin before 16 years of age, and last in excess of more than 6 weeks (1). With a reported prevalence of 86.1-94 per 100,000 children (20), JIA is the most common childhood chronic rheumatic disease and one of the leading causes of paediatric acquired disability (2;4;5).

The term JIA encompasses several disease categories, each of which has distinct methods of presentation, clinical signs, and symptoms, and, in some cases, genetic background. The disease is characterized by chronic inflammation of the joints and, in some patients, extra-articular manifestations including uveitis (iridocyclitis) or systemic features such as high fever, lymphadenopathy and serositis. The cause of the disease is still poorly understood but seems to be related to both genetic and environmental factors, which result in the heterogeneity of the illness.

JIA classification identifies different categories, many of which appear to represent different diseases characterized by distinct modes of presentation, clinical features, and, in some cases, genetic background. Seven categories are currently reported in the International League Against Rheumatism (ILAR) classification (21;22): s*ystemic arthritis (*arthritis, fever, rash etc), o*ligoarthritis* (four or less joints affected during the first 6 months of disease) which is further divided into two subsets: *persistent* (if the arthritis remains confined to four or less joints) or *extended* (if arthritis extends to more than 4 joints after the first 6 months of disease), *rheumatoid factor (RF) positive polyarthritis* (five or more joints involved during the first 6 months of disease and positive RF; it is the equivalent in childhood of adult RF positive rheumatoid arthritis); *rheumatoid factor* negative polyarthritis (five or more joints involved during the first 6 months of disease in the absence of RF), *enthesitis-related arthritis* (association of enthesitis and arthritis; these patients are often HLA B27 positive and share many features in common with adult spondyloarthropathies), *psoriatic arthritis* (simultaneous presence of arthritis and a typical psoriatic rash or of a series of psoriatic features), and *undifferentiated arthritis* if it does not fit any or fit more than one of the previous.

In this application we will distinguish the following categories of JIA as follows: **oligoarticular course** (less than 5 active joints), that usually is not treated with MTX or biologic agents, JIA with **polyarticular course** (at least 5 active joints) that is the usual target of second line therapy, and **systemic arthritis** that encompass a disease subgroup with different pathogenetic characteristics and treatment modalities.

Current available guidelines for treatment of children with JIA

Several guidelines for treatment of children with JIA currently are available (23).

The goal of therapy in oligoarticular course JIA is essentially to induce a clinical remission off medication mainly through the use of intra-articular joint injections with or without the use of concurrent NSAIDs. Systemic therapies are generally considered only in rare cases in which one or more courses of joint injections are not effective.

The goals of therapy in polyarticular course JIA and in systemic JIA are several and can be summarised as follow:

- short term: achievement of response to therapy according at least to the ACR Pediatric 30/50 criteria (24-26) or the attainment of a status of minimal disease activity (MDA) (27)
- long term goals:
  - achievement of clinical remission on and then off medications (28;29)
  - prevention of joint erosions (30-34)
  - prevention of flare of the disease (10-15;35)
  - attainment of good health related quality of life (HRQOL) (2;3;5;6;36).

Attainment of the above goals is usually pursued with a hierarchical use of several drugs alone or in combination as briefly described previously.

Regulatory status for JIA and other PRD treatments

Among the biological drugs presently available for the treatment of JIA only etanercept, adalimumab and abatacept are currently authorized for use in JIA by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA).

Despite the efficacy and safety data available and the current medical practice, MTX is registered in the US but not in most countries in Europe. Therefore, MTX is largely prescribed off-label worldwide.

JIA REGISTRY METHODOLOGY

Introduction

In order to establish the long-term safety and efficacy (response, joint erosion, damage, and treatment adherence) of biologic agents and MTX in JIA, e.g. the extent to which these drugs do more good than harm under the usual circumstances of healthcare practice in JIA, we plan to implement an observational registry including all children with JIA treated with any available MTX and biologic agents formulation. The registry aims to observe these paediatric population over at least 3 years with a possible extension beyond the 3 years if adequate funding will be available.

Rationale

We aim to assess the long-term safety (primary goal) and effectiveness (magnitude of response, prevention or slowing of joint erosions, damage, and treatment adherence) of MTX and biologic agents in JIA. There are data to suggest that there is a therapeutic window early in these diseases during which the probability of a favourable response is increased. We also aim to determine evidence for the existence of such a window of opportunity.

Hypothesis to be tested

The overall hypothesis is:

- Biologic agents ± MTX agents are able to maintain an acceptable safety profile in the long term in children with different JIA categories while achieving clinical remission and prevent/stop joint erosion development over time.

The overall aims are to establish the long term safety of biologic agents and MTX, and their relative effectiveness in children with JIA who need treatment with second line agents.

Setting. Centres belonging to PRINTO/PRES networks

Primary objectives

- To compare the long term incidence rates of emergent moderate, severe adverse events (AEs) and serious A (SAE) observed in paediatric subjects with JIA.
- To assess the long-term efficacy (magnitude of response, prevention or slowing of joint erosion and damage, and treatment adherence) of biologic agents±MTX in paediatric subjects with JIA.

To accomplish these objectives we will establish 3 different cohorts (treated with either MTX alone, biologics with or without concomitant MTX, or not treated with MTX or biologics). Each cohort will be used as a comparator for the others. (37)

Secondary objectives

- To identify predictors of safety (clinical or experimental, magnitude of response, remission)
- To assess potential risk factors (e.g. concomitant medications or diseases, medical history etc), which may modify the safety profile of biologic agents and MTX;
- To evaluate efficacy in terms, in the different JIA categories, of individual JIA core set variables, and the ACR Paediatric 30, 50, 70, 90, 100 criteria for improvement, and the achievement of clinical remission on and off medication as well as the occurrence of disease flare during biologic agents and MTX treatment course and after drug discontinuation, and the attainment of a status of MDA;
- To assess the number of children in which a biologic agent is added to the treatment.
- To evaluate the progression of wrist joint erosion over time and abnormal growth/maturation in JIA subjects presenting a wrist involvement.
- To assess the reasons for stopping drug treatment.

Primary endpoint.

Safety

- Proportion of JIA paediatric subjects with biologic agents and MTX -emergent moderate/severe and SAEs, referred as all moderate/severe AEs and SAEs belonging but not limited to events of special interest (ESI) such as malignancies (37-41) and inflammatory bowel disease and other such as opportunistic infections, autoimmune events, cardiovascular events, central nervous system involvement (e.g. optic neuritis, demyelinating disease), infertility, gastrointestinal bleeding, macrophage activation syndrome (MAS) (42);

Efficacy

- ACR Pediatric 30, 50, 70, 90, and 100 criteria for improvement
- Clinical remission remission on and off medication according to the CARRA/PRINTO/PRCSG criteria (28) as well as MDA;
- Improvement of individual JIA core set variables (physician's evaluation of disease activity, parent's evaluation of overall well-being, Number of active joints, number of joint with limited range of motion, index of inflammation, index of inflammation either ESR or CRP, fever), and the Juvenile Arthritis Disease Activity Score (JADAS) (43);

Secondary Endpoints

- Three to 10-year and longer probability of not experiencing AEs.
- Incidence rate of biologic agents and MTX-emergent moderate/severe AEs and SAEs in the 3 comparator groups.
- Treatment adherence and reasons of treatment withdrawal/change (e.g. lack of efficacy, AE and SAE or add-on therapy for inefficacy/intolerance, remission)
- Time to flare (as per standard PRINTO flare definition) (10-15;35) during biologic agents and MTX treatment course and after biologic agents and MTX discontinuation.
- Joint space erosion over time (if part of routine care) according to the Poznanski score and erosion score according to the adapted versions of the Sharp/van der Heijde score at months 12 and 24 (30-34).
- Baseline clinical and demographic predictors of safety (either clinically or laboratory), response, remission.

Study Design

This is a 3-10 year, international, multicentre, observational, safety and efficacy (response, joint erosion, damage, and treatment adherence) study aimed at collecting prospective safety, tolerability, efficacy, and treatment adherence information on JIA subjects exposed to any biologic agents and MTX, according to local standard of practice.

This is a ***non-interventional study,*** where the medicinal products are prescribed as per the investigator's decision. The assignment of the subject to a particular therapeutic strategy is not decided in advance by the study protocol, but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the subject in the study. No additional diagnostic or monitoring procedures shall be applied to the subjects and epidemiological methods will be used for the analysis of collected data.

Duration and treatment will be as per investigator's decision. The nature and frequency of subjects' visits to the investigator's site will be determined only by the investigator, according to his/her judgment on the basis of the clinical evolution of the subject.

The duration of the study is expected to be at least 3 years from initiation of the first site and may be continued beyond if adequate funding is be available.

Population

JIA (any ILAR category) after proper consent/assent. Two specific populations will be enrolled (Figure 1):

- **Prevalent cases** all patients under treatment or previously treated with biologic agents ± MTX, MTX alone or biologic agents alone or treated only with NSAIDs and/or steroid injection at the time of project start will be revised retrospectively to estimate moderate moderate/severe AEs and SAEs. The same patients will be continued to be followed over time after proper written informed consent.
- **Incident case.** All cases newly treated with biologic agents±MTX since the registry start.

From a time perspective the data collected will be (Figure 1):

- Retrospective chart review of safety data.
    - **Step 1:** A census (e.g. collection of patient identification number, age, JIA type and type of treatment) will be required from each centre before retrospective chart review of safety data initiation to avoid selection biases (e.g. to have the proper denominator against which evaluating the successful data collection).
    - **Step 2:** Retrospective chart revision for the collection of moderate/severe AE and SAEs until the time of the last available visit. This retrospective chart review will be considered successfull if at least 70% of the patients listed in the census will be retrieved. This step will include also the integration in the Pharmachild project, of data collected by other ongoing national registries (e.g. German, UK, French, Italian, USA etc) (44-47).
- Prospective safety/efficacy data collection. This group will include patients newly treated with biologic agents±MTX and patients already on treatment and still followed at the participating centres and identified with the retrospective chart review.

Exposure

a) **Medicinal Product (**biologic agents ±MTX)**:** prescribed according to treating physician's decision. Dose, frequency and route of administration will comply with local standard of practice.
b) **Co-medications:** NSAIDs, systemic, intra-articular CS, and folic acid or its derivatives whose dose, frequency and route of administration comply with local standard of practice.

Inclusion criteria

- Signed written informed consent by subjects and /or parent or legally acceptable representative
- JIA (any ILAR category).
- Subjects receiving biologic agents ± MTX, MTX alone, or NSAIDs and/or steroid injections only as per physician discretion.

Choice of the comparator group

Three main groups of patients will be identified, each one serving as comparator group for the remaining groups (Figure 1):

1. JIA treated with biologic agent alone or MTX alone;
2. JIA treated with a combination of biologic and MTX (including any other add on therapy e.g. cyclosporine, leflunomide etc);
3. JIA treated only with NSAIDs and/or steroid injections with at least 3 years follow-up.

Group 1 and 2 mainly refer to children with polyarticular course JIA treated with MTX ± biologics, while group 3 refers to children with mostly oligoarticular persistent course who are usually NOT treated with second line agents and have a more benign course. The 3 groups of children will constitute the ideal comparator groups for any future evaluation of the incidence rate of serious adverse events for whom safety concerns (mainly cancer) have been raised by the FDA (38;48;49) and other (50-53).

Suggested schedule of assessment

Table 1 shows the suggested scheduled of assessments for the retrospective (one time assessment at the last available visit) and prospective cohorts (dld cases still in follow up every 6 months or according to local practice for newly treated incident cases baseline, 3, 6 and then every 6 months OR according to local practice). However, local clinical practices differ in their suggested schedule of assessments, so the frequency of procedures may be different (e.g. every 6 months and then annually). The retrospective cohort will require completion of a safety assessment only.

PROCEDURES FOR THE SUCCESS OF THE PROJECT

Methodological plan for patient and physician's retention in the protocol

The plan is to collect moderate/severe AE and SAEs, as well as efficacy data, on a long term basis (up to 3-10 years). For this reason it is our strong belief that the key to success of the registry, is a worldwide participation extended to the entire PRINTO/PRES membership, with strong motivation by each of the participating physicians and by all families of the children involved.

In order to reach the above goals one fundamental aspect is to simplify data collection as much as possible while maintaining scientific integrity (few key data are better than no data principle) (54). For this we will implement several strategies as briefly outlined here:

1. Before the official start of data collection a specific census log for all the patients previously treated with MTX ± biologics at that specific centre will be required. The census log will contains minimal information such as PRINTO ID, JIA category, drug treatments). This will be the reference against which we will be able to evaluate if indeed the centres will submit all or most of the cases treated with MTX ± biologics. In addition we plan to collect also few key elements (essentially safety) for children with oligoarticular persistent JIA who normally are NOT treated with MTX ± biologics or other second line agents. This will constitute the ideal comparator group against which to evaluate the MTX ± biologics safety profile (Figure 1).
2. Limit data collection to the essential key elements (JIA core set variables and AE classified greater than or equal to moderate). The simplest and more user-friendly Juvenile Arthritis Multidimensional Assessment Report (JAMAR) (55) questionnaires will be used for the data collected by parents/children.
3. Collect more detailed information on key expected SAE. The web system will be modular and upgradable on as per needed base so that PRINTO can require to collect related specific information in the event of unexpected SAE. The Medical Dictionary for Regulatory Activities (MedDRA) will be the standard dictionary for AE data collection.
4. Implement a system by which physicians can collect via the web system the related data during the routine follow up visits of the patients via the web system. The plan is to set up a user-friendly and simple system which will provide a detailed report of the efficacy and safety data in a few minutes (ACR response, flare, clinical remission, JADAS score, safety summary) to be stored in the chart of the patients as a PRINTO report. The system will also provide a quantitative graphical depiction over time of the key efficacy data (e.g. JADAS).
5. Involve data collection from all families with internet access who will consent to provide their personal contact information including 1-2 relatives (e-mail essentially) to access the PRINTO web system in the family dedicated section. In this area volunteering families or children can report safety concerns as well as complete the simplified but scientific rigorous parents/children reported outcome (JAMAR) (55-57). These data will be required to be completed before the scheduled clinic visit so as to provide key notes to the treating physician. If available on site, access to internet (e.g iPAD or similar) or paper forms will be provided to families with no internet access to record the occurrence of AE in the months at the time of the scheduled clinic visit as well as the patient's reported outcome and then entered on the web-system.
6. Both physicians (in English medical terminology) and families (in translated plain text) will be regularly updated (e.g. at least yearly) about the safety and efficacy issues concerning drug administration with general and specific (addressed to each individual doctor or family emails) electronic newsletters.
7. Electronic reminders to complete the physicians/families CRF will be sent to registered users on the PRINTO website.
8. The web-database will be developed by PRINTO (certified ISO 9001:2008) following its internal SOP for database development.

9. Regular meetings will be held among the responsible individuals of the major national registries in Europe and outside which will agree to participate to the project (e.g. Germany, UK, France, Netherlands, Spain, Czech Republic primarily) (44-47). The goals of these meetings will be to agree on the proper way to share common data essentially for safety reasons for example in all patients under treatment or previously treated with biologics ± MTX. A meta-analysis of the data already collected by the national registries will be set up in order to establish a consolidated paediatric rheumatology registry. The meeting will be opened to representatives from North America in order to strengthen the transatlantic collaboration and possibly joint data also with them: e.g. the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Childhood Arthritis and Rheumatology Research Alliance (CARRA).

PRINTO feasibility surveys

Prior to developing this protocol, PRINTO conducted a feasibility survey among the centres belonging to the PRINTO/PRES network. Table 2 (PRINTO feasibility survey results) shows the number of JIA patients under treatment or newly treated with MTX ± biologics within the PRINTO network in year 2008 as of November, 2009 (with update in 2010). A total of 205 PRINTO centres in 52 countries expressed their interest to participate to the project (40 refused to participate). The total number of patients under treatment with MTX in year 2008 was 21,421 (prevalent cases) with 4,858 being the subgroup of newly treated patients.

The feasibility will be updated at the time of census (see step 1 for retrospective data collection).

The total number of patient under treatment with biologics in year 2008 was 7,912 (prevalent cases all biologics combined) with 2,717 being the subgroup of newly treated patients.

Our goal is to involve only large centres who treat at least 100 JIA patients. The total number of patients potentially eligible for enrolment is 10,000 patients who are being followed by 100 researchers in 100 different PRINTO centres who have been followed for 5 years (100/6000 person months)

OTHER GENERAL ISSUES

Time oriented table

See Table 3

Age group

Children with JIA (any ILAR category) will be enrolled. Second line agents are now prescribed in JIA in any age class but children < 1 years are very rarely treated with such agents.

Drug for joint injections

Since it is standard practice to perform joint injections in JIA, all children needing this procedure might receive intra-articular triamcinolone hexacetonide (58-64) at the discretion of the paediatric rheumatologist.

Tools to be used to assess functional ability (disability) and quality of life

As part of the JAMAR (55) two new, simple and short questionnaires for the evaluation of functional ability (disability) and quality life named Juvenile Arthritis Functionality Scale (JAFS) (56) and Pediatric Rheumatology Quality of Life Scale (PRQL) (57) will be used.

Clinical and laboratory evaluations

These include the complete physical examination and rheumatological joint count. No specific laboratory tests will be required for the registry, other than the usual laboratory testing performed according to local clinical practice.

Biologic sample collection for research purposes

Specific research project(s) requiring the collection of biologic samples including but not limited to serum, plasma, DNA/RNA might be implemented during the course of the project to explore specific research questions. For these sub-project(s) an amendment will be put in place for all participating centres with an appropriately worded informed consent/assent document.

Treatment failures and withdrawal from the registry

Patients will be considered "treatment failures", if any of the following will occur at any time during the study.

1) For the prospective cohort patients who will need, besides MTX ± biologics, additional drug treatments (e.g. other additional DMARDs) or switch to another DMARD at any time after drug start, or who discontinue for safety reasons/attainment of clinical remission. Patients will continue to be followed for safety reasons for the entire duration of the registry.
2) Patients are withdrawn from the study at any time based on family decision.
3) The attending physician will determine, clinically, if a patient should be removed from the study.

Procedures to follow to report a moderate/severe AE and SAE

In the event of a moderate/severe AEs and SAE, the attending physician should make the clinical decision as to which medication is most likely the cause of the AE, and decide about drug continuation. The attending physician will be responsible for reporting ALL clinically significant moderate/severe AEs and SAE, and the relationship to the study medication. Mild AEs will not be recorded to lessen the burden of data collection while maintaining scientific integrity.

PRINTO will regularly notify investigators, ethics committee, regulatory authorities or pharmaceutical companies for all SAE reported by the investigator in the PRINTO web database.

Informed-Consent/assent documentation

Ethics Committee approved informed-consent/assent will be obtained from parents/legal representative or children of an appropriate age (translated into the applicable national language) for the prospective cohort while the retrospective cohort (Step 1 and 2) will be collected anonymously and consent requested only if required by the local ethics committee. An important aspect of success of the prospective data, if allowed by the local Ethics Committee, will be the collection of contact information (emails essentially) of the family plus 1-2 relatives (e.g. grand-parents, uncles) in order to properly track the possible move of the family (to other hospitals); such personal information will be kept just by PRINTO and not shared with anyone else. At the time of the analysis all patient data will be de-identified.

IMPORTANT: the personal information (first and last name, date of birth and the national patient unique identifier) will be seen ONLY on the local computer screen. The PRINTO web system will automatically ENCRYPT the personal data and ONLY the encrypted data will be saved on the on the PRINTO central database on an https platform.
The PRINTO website will automatically assign a patient number (PRINTO patient id) to be used for communication with the centre.
The PRINTO encrypting algorithm is designed in a way by which it is impossible for PRINTO to decrypt the personal information and disclose to anyone the patient first/last name, the date of birth and the national patient unique identifier.

Data Collection

Data will be collected on line via the secured PRINTO website on a dedicated server with a username and password access only on an https platform (technical management of the database by the PRINTO webmasters will use an encrypted platform with a customized database). Specific agreements will be put in place with existing national registries to combine the data into a common database. English will be the official language used for all forms completed by the physicians, while forms filled by parents/patients will be translated into the appropriate national language.

Random remote monitoring, quality Assurance

All forms will be reviewed by the PRINTO Coordinating Centre for completeness and report of moderate/severe AE and serious AEs.

A random remote monitoring of 5% of consent forms and case report forms will be completed by the PRINTO coordinating centre in collaboration with the individual participating centres and the help of the PRINTO national coordinators (list at www.printo.it). Centres subject to random monitoring will be asked to send to PRINTO copy of the original source document for data source verification. The project will rely only on highly qualified centres.

STATISTICAL ANALYSIS

Analysis will be mainly descriptive in nature. For continuous numeric data (e.g., baseline demographic data such as age), the descriptive statistics including number of subjects (n), mean, standard deviation (SD), median, and inter-quartile ranges will be summarized by dose group. For categorical data, the frequency count will be presented by dose group.

Safety and tolerability will be summarized by treatment group. The number and percentage of subjects experiencing treatment emergent adverse event will be summarized by system organ class, preferred term, and treatment group. The number and percentage of subjects with clinically important laboratory abnormalities and vital signs measurements during the treatment period will be summarized by dose.

Concomitant medications will be tabulated by generic drug name. Moderate/severe AEs and SAEs will be coded according to the current version of MedDRA.

In order to avoid information biases the JIA ILAR classification criteria will be used for patient identification. A census, as previously described will be implemented to avoid selection biases. In order to take into account possible effect modifiers 3 comparator groups have been chosen (see previous section)

All scientific reporting in medical journals will be as per the CONSORT statement (65;66). Qualitative data will be compared by chi-square test or by Fisher's exact test. In case of multiple comparisons, Bonferroni correction will be applied. Quantitative variables among different groups of observations will be compared by means of the Kruskal-Wallis test; the Mann-Whitney U test with Bonferroni correction will be used as a posterior test. All tests will be 2-sided and a P value less than 0.05 will be considered statistically significant.

Non parametric ANOVA will be applied in case of ordinal data or not-normally distributed variables with proper a posterior tests. Treatment effect size will be calculated by dividing the difference between the baseline and the final visit value, by the standard deviation of the first visit value. For multiple hypothesis testing, alpha level is set at 0.01. All analysis will be done in a blinded manner with the statistician who will perform the analysis blinded to treatment groups etc.

Primary Endpoints analysis

All moderate/severe AE and SAEs (including those leading to MTX or biologic treatment discontinuation) will be summarized per patient year of follow-up, describing the relationship to the treatment.

- The AE incidence rate by drug will be estimated after partitioning the follow-up periods of each patient into subintervals corresponding to the administration of the drug, with any event being attributed to the drug itself. This implicitly assumes the independence of the outcome in different subintervals pertaining to the same patient.
- Relative risk will be calculated to compare the primary AE rates with the remaining comparator groups (see previous section). As possible covariate for the analysis JIA category, gender, age and drug use history will be considered.

The 3 to 10 year probability of not meeting toxicity criteria (see AEs of special interest) will be estimated.

Secondary Endpoints analysis

- Maintenance on the originally administered biologic agents±MTX formulation will be evaluated as the number of days from treatment start to treatment discontinuation, which could lead to the switch to another therapy or the add-on of another drug or drug withdrawal for safety, remission etc.

- As a treatment may have been discontinued for various reasons (lack of efficacy, adverse event, inactive disease or other), the crude cumulative incidence (CCI) of discontinuations for each reason will be computed and the treatments compared (67;68)(25, 26).

Time to moderate/severe AE or SAE occurence

To be evaluated as the number of days from treatment start to the event occurrence, and probability estimated (10-15;35).

Interim analysis

Preliminary analyses are planned every year with analysis of AEs incidence rate. Rate comparison with the comparator cohort will be performed after enrolment of 50% of the estimated sample and at the end of the study.

Sample size:

The sample size calculation is based on data derived from a MTX and biologics 3-year observational study (69).

Assumptions:

- Total number of AE (any AE) n (%) in MTX treated group 71/197 (0.36)
- Total number of subject without AE in the MTX treated group: 1 – 0.36= 0.64
- Total number of AE (any AE) n (%) in MTX plus biologic or other drugs treated group 137/294 (0.466).
- Total number of subject without AE in the MTX plus biologic treated group: 1 – 0.466= 0.534
- Hazard ratio (MTX/MTX plus biologic) logn 0.64/logn 0.534=0.711

	Hazard ration	Alfa	Power	Number AE to be observed	N per 2 arms	Drop out N/(1-0.2)
MTX versus MTX plus Biologics	0.711	0.05	0.8	271	670	838
MTX versus MTX plus Biologics	0.711	0.05	0.9	362	896	1,120

Notes: Two sided-test; Software nquery v 7 (70).

ADDITIONAL INFORMATION

Regulatory documentation
Every effort will be done to involve as much as possible regulatory authorities (FDA and EMA) during the finalisation of the current protocol as well as during the analysis phase and for the direct use of the data collected for regulatory purposes.

Liaisons and content of the future agreement with other registries
An important aspect for the success of the project will be the liaison and formal agreements with available JIA registries (e.g. Germany, UK, France, Netherlands, Spain, Czech Republic, United States primarily) (44-47).
An agreement will be reached with each registry to establish common rules for data sharing.

The general principles for such agreements will be:

- the other registries will have to agree to combine their effort with the overall PRINTO/PRES registry;
- the other registries will maintain the right to access and manage all data collected within the border of country belonging to that registry through specific ad hoc web authorisation;
- the other registries will maintain the right to publish by using all data collected within the border of country belonging to that registry;
- for the purposes of combined publication using all data available in the PRINTO/PRES registry, data will be anonymised and authorship decided according to the PRINTO policy for authorship proportional to the contribution of each centre/other registry.

Liaisons and content of the future agreement with pharmaceutical companies
In the event pharmaceutical companies intend to use the data collected with this registry, a formal agreement will need to be reached with PRINTO.

- A statement that companies intend to use the data derived from project for regulatory post-marketing surveillance obligations related to their products. Type of data to be used:
    - Data derived from the current registry
    - Request to collect specific ad hoc additional data (e.g. through separate protocol/sub-study and specific consent).
- Use for marketing purposes limited to published data or after ad hoc agreement

In either case an amendment to the current protocol will have to be submitted to the ethics committees of each participating centre.

- Companies will acknowledge that PRINTO will maintain ownership of the data and will be totally free to use such data for scientific purposes. Companies will have the first right to buy the data derived by the project at a market price from PRINTO for use in regulatory submissions or other purposes. Market price will be established based on the cost incurred for the implementation of this project. As per standard PRINTO policy, all related possible future revenues from companies will be totally reinvested for the research needs of the project (e.g. no money to be used for personal gain) and, in particular, to support the prolongation of the registry over the planned 3-10 years. Data that is presented to the public or published in the professional literature can be used by companies without payment.

Financial compensation.

Centres which succeed in providing the requested data (census, prevalent and incident case) will be entitled to a reimbursement based on a fee per each valid patient entered into the registry, and a fee for each visit.

At the time of the current protocol funding derive from a 3 years EU grant (2011-2014) entitled "Long-term PHARMacovigilance for Adverse Effects in Childhood Arthritis focusing on Immune Modulatory Drugs" (project number 260353). This funding will be allocated to data collection limited to the group of patients treated with biologic agents on a competitive fashion and proportionally to the contribution of each centre. A separate contract with details related to payment will be put in place for each participating centre. Based on funding allocation a total up to 3000 patients are expected to be enrolled.

In the event that a contract is established with a pharmaceutical company, or other funding becomes available, the additional revenues will be used to support further data collection (e.g. patients treated with MTX monotherapy, patients treated with NSAIDs). An amendment and a related contract will then have to be implemented with each participating centre.

In all remaining cases, data contributions to the registry will be voluntary by the PRINTO/PRES members.

Writing committee of the protocol.

The protocol has been drafted by the PRINTO Senior Scientist (Nicolino Ruperto, MD, MPH) with the PRINTO staff (Angioloni Simona, BA, Pallotti Chiara, MA, Luca Villa, BA, Michele Pesce, BA) and critically revised by the PI of the Pharmachild grant (Nico Wulffraat, MD, MPH) and by the PRINTO Chairman (Prof. Alberto Martini, MD).

Versions of the protocol have been also revised by the Pharmachild partners (Gerd Horneff, Kath Watson, Michael W Beresford, Kirsten Minden, Wendy Thomson) and by the Pediatric Rheumatology Collaborative Study Group (PRCSG, Daniel J. Lovell, MD, MPH, Hermine Brunner, MD, MSc, MBA, Edward H. Giannini, MSc, Dr.PH).

The protocol and CRF has also been shared with members of the Childhood Arthritis & Rheumatology Research Alliance (CARRA, Christy Sandborg, MD, Yukiko Kimura, MD)

APPENDIXES

Glossary for moderate/severe AE and SAEs.
Physicians will be required to report **MODERATE/SEVERE AE and SAE** the patients experienced since the disease onset.
IMPORTANT: Mild adverse event (e.g. discomfort noticed but no disruption of daily activities) ***SHOULD NOT BE REPORTED***
Definitions:

- **Moderate adverse event**: discomfort sufficient to reduce or affect daily activity
- **Severe adverse event:** inability to work or to perform normal daily activity
- **Serious adverse event**: one of the following:
  a. Death
  b. An adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred
  c. Inpatient hospitalization or prolongation of existing hospitalization
  d. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  e. A congenital anomaly or birth defect
  f. An event that, based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described above (items a-e)

MODERATE/SEVERE AE and SAE should be coded as per the appropriate medical dictionary for regulatory activities (MedDRA) terminology (more info at http://www.meddramsso.com/). The MedDRA hierarchy is as follows:

MedDRA HiERARCHY	EXAMPLES
SYSTEM ORGAN CLASS (SOC)	**SOC:** Blood and lymphatic system disorders
HIGH LEVEL GROUP TERM (HLGT)	**HLGT:** Lymphomas Hodgkin's disease
High Level Term (HLT)	**HLT:** Hodgkin's disease lymphocyte depletion type
Preferred Term (PT)	**PT:** Hodgkin's disease lymphocyte depletion state I site unspecified
Lowest Level Term (LLT)	**LLT:** Hodgkin's disease lymphocyte depletion state I site unspecified

Current glossary for the evaluation of response to treatment

In 1997 PRINTO, under the guidance of Prof. E.H. Giannini of the Pediatric Rheumatology Collaborative Study Group (PRCSG), published criteria to evaluate response to therapy in JIA that that are now known as **American College of Rheumatology (ACR) Paediatric 30 criteria** (ACR Paed 30) (24-26). According to the ACR Paed 30 patients are considered responders to a given therapy if they demonstrated at least 30% improvement from baseline in at least 3 of any 6 JIA core set variables with no more than 1 of the remaining variables worsened by more than 30%. The ACR Paed 30 allows researchers or clinicians to dichotomize patients into responders or non-responders. Patients are usually also evaluated for ACR Paed 50, 70, 90 and 100 criteria (at least 50-70-90-100% improvement, respectively, in at least 3 of any 6 JIA core set variables with no more than 1 of the remaining variables worsened by > 30%). The individual validated JIA core set variables included: the number of joints with active arthritis (defined as a joint with swelling or, if no swelling is present, a joint with pain and limitation on movement) (range 0-71) (71;72); the number of joints with limited range of motion (range 0-67) (73;74); the physician global evaluation of disease activity on a double anchored 21 circle visual analogue scale (VAS) (anchoring words: 0=no activity, 10=maximum activity); the parent assessment of child's overall well-being on a double anchored 10 cm VAS (anchoring words: 0=very well, 10=very poor); functional ability (disability) usually measured by the disability index of the Childhood Health Assessment Questionnaire (CHAQ) (75-77); an index of inflammation (the Westergren erythrocyte sedimentation rate (ESR) or the C reactive Protein (CRP). These criteria are now accepted also by the Food and Drug Administration (FDA) and the EMA for all phase III JIA trials seeking registration, has been endorsed by the ACR and has been pivotal for all trials with biologic agents and MTX (8;10-15).

In 2002 Brunner et al defined (35) a **JIA flare** as ≥30% worsening in at least three of six JIA core response variables and ≥30% improvement in no more than one variable during the double-blind period. Subsequently some contingencies were added requiring that if the physician or parent global assessment was used to define flare, a ≥20 mm worsening on the 100 mm VAS was required; worsening in ≥2 joints was required if the number of active joints or joints with limitation on motion was used. These criteria have been pivotal for all trial using randomized double blind withdrawal design (10-15).

In 2004 the Childhood Arthritis and Rheumatology Research Alliance (CARRA)/PRINTO/PRCSG also defined **JIA inactive disease** status (28;29) as follows: no joints with active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA (for systemic JIA patients); no active uveitis (glossary to be defined); normal ESR or CRP (if both are tested, both must be normal); physician's global assessment of disease activity indicates no disease activity (i.e., best score attainable on the scale used or ≤ 0.5 cm on a 0-10 scale) and morning stiffness ≤ 15 minutes.

Two types of clinical remission definition were proposed:

a) **clinical remission on medication** in which the criteria for inactive disease must be met for a minimum of 6 continuous months while the patient is on medication in order for the patient to be considered to be in a state of clinical remission on medication;
b) **clinical remission off medication** in which the criteria for inactive disease must be met for a minimum of 12 continuous months while off all anti-arthritis and anti-uveitis medications in order for the patient to be considered to be in a state of clinical remission off medication.

In 2008 Ravelli et al proposed a definition of **minimal disease activity (MDA)** in JIA (27) that could be defined as the presence of a physician global assessment <2.5 cm and a swollen joint count of 0 in patients with oligoarthritis; and as the presence of a physician global assessment <3.4 cm, a parent global assessment < 2.1 cm, and a swollen joint count < 1 in patients with polyarthritis.

More recently PRINTO also proposed a measure to quantify the level of disease activity known as the validated **Juvenile Arthritis Disease Activity Score** (JADAS) (43) which results from the arithmetic sum of the scores of 4 individual component: the physician and parent/patient global

assessments (both measured on a 0-10 cm VAS), the joint count (78) and ESR value converted to a 0-10 scale.

Similarly they also contributed to standardise the evaluation of **joint erosions** in JIA through conventional radiography (Poznasky and Sharp/van der Heijde score), (30-33) ultrasonography and magnetic resonance imaging (34) and to prepare shorter and simpler questionnaire for the evaluation of functional ability (disability) and quality life named Juvenile Arthritis Functionality Scale (JAFS) (56) and the Pediatric Rheumatology Quality of Life Scale (PRQL) (57) now part of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) (55) .

FIGURES AND TABLES

Figure 1: study design

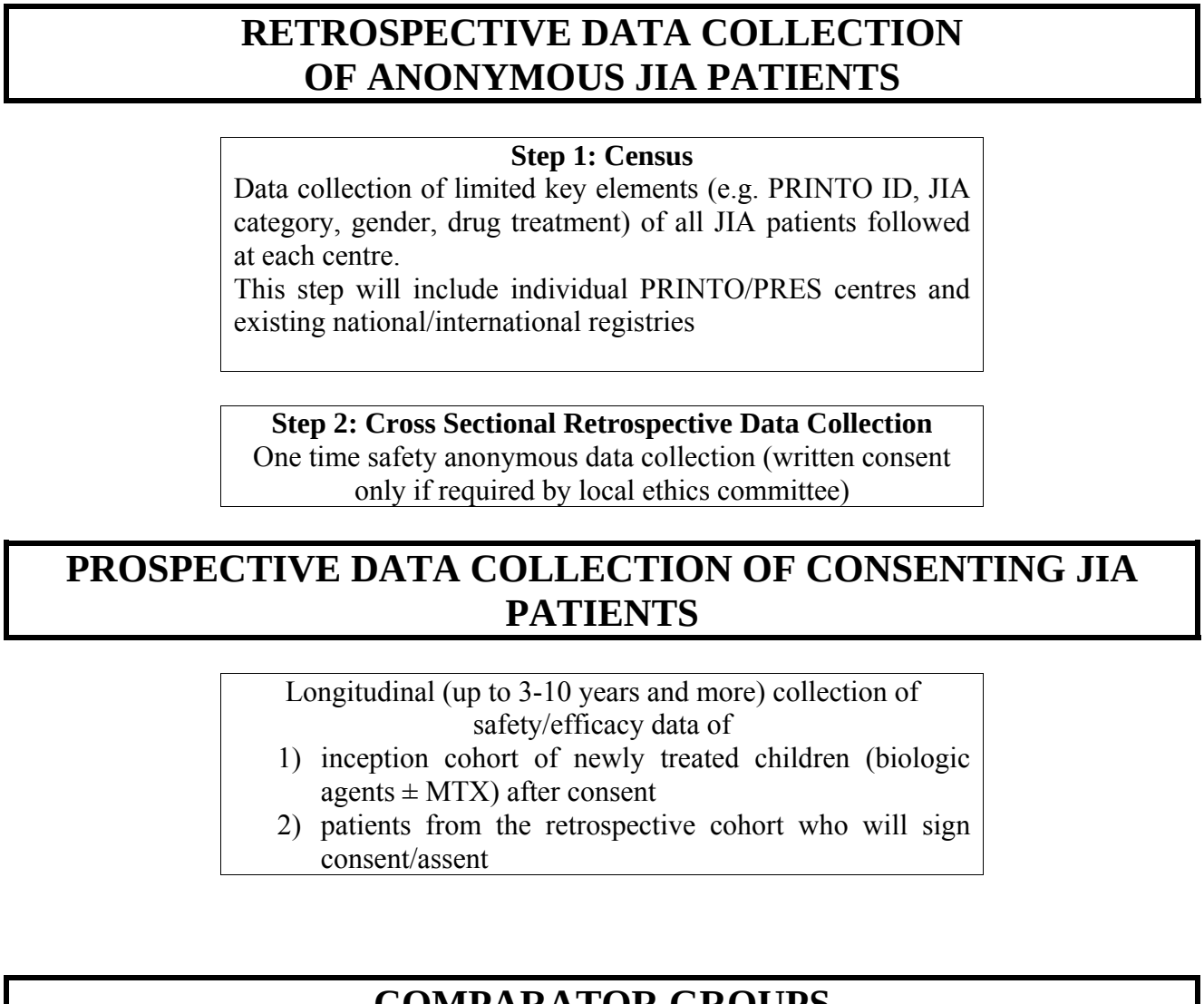

Table 1: Study Procedures and Data Collection*

	Baseline	Suggested schedule: month 3, 6, and every 6 months thereafter OR according to local practice	At Time the Assessment Takes place or the Event Occurs
Prevalent cases[a]			
Informed consent[b]	X		
Demographics	X		
Moderate, severe or serious adverse events	X		
JIA related therapies	X		
Incident cases			
Informed consent/assent	X		
Height, weight	X	X	X
Moderate, severe or serious adverse events		X	X
JIA related therapies	X	X	X
JIA core set[c]	X	X	X
Optional assessments			
JADI[d]	X	X	X
X-rays[d]	X	X	X
Tanner Sex Stages	X	X	X
Biologic samples in selected centres[e]	X	X	X

*This is the proposed scheduled of assessments. However, local clinical practice may mandate that the schedule of assessments be different (e.g. every 6 months and then annually). In such cases the local schedule will be followed.

[a]For prevalent cases data collection will be done once at the time of the centres clinical chart revision

[b]data will be collected anonymously: consent from parents will be required only if necessary by the national laws

[c]ESR or CRP only if performed as per standard local practice.

[d]JADI, wrist and hand x-Rays, Tanner stages annually only if performed as part of routine care

[e]Biologic samples for immuneregulation assays will be performed only in a subset of patients followed in ad hoc selected centres

Table 2: PRINTO Feasibility Survey Results

Results of a survey performed within the PRINTO network. The purpose was to estimate the number of JIA patients under treatment (prevalent cases) or newly treated (incident cases) with MTX and other biologic agents in year 2008. Results as of November, 2009 (with update 2010) in 205 centres in 54 countries

Country	Number of centres	MTX total	MTX new	ETN total	ETN new	INF total	INF new	ADA total	ADA new	ABA total	ABA new	ANA total	ANA new	Other total	Other new
1. Albania	1	12	0	0	0	0	0	0	0	0	0	0	0	0	0
2. Argentina	9	839	185	206	62	53	10	35	17	25	22	3	3	7	5
3. Australia	4	675	100	180	45	23	8	4	4	0	0	10	7	7	7
4. Austria	5	287	50	63	25	6	2	7	3	0	0	5	4	0	1
5. Belgium	3	145	27	38	12	0	0	9	5	0	0	6	0	8	8
6. Bosnia and Herzegovina	1	7	15	2	0	0	0	0	0	0	0	0	0	0	0
7. Brazil	9	817	275	110	60	63	21	46	24	22	12	3	3	6	6
8. Bulgaria	1	110	15	31	12	2	0	0	2	0	0	0	0	0	0
9. Chile	2	59	12	6	2	2	1	2	1	0	0	0	0	0	0
10. China	1	120	50	20	15	0	0	0	0	0	0	0	0	0	0
11. Colombia	2	95	28	38	13	3	3	0	0	0	0	0	0	1	1
12. Costa Rica	1	40	11	3	3	0	0	0	0	0	0	5	0	0	0
13. Croatia	3	180	85	42	23	18	11	0	3	1	0	0	1	0	0
14. Czech Republic	1	250	50	70	20	0	0	10	4	0	0	0	0	0	0
15. Denmark	2	720	130	152	48	49	20	78	36	2	2	8	5	3	3
16. Egypt	1	24	6	0	0	0	0	0	0	0	0	0	0	0	0
17. El Salvador	1	80	12	8	4	0	0	0	0	0	0	0	0	0	0
18. Estonia	1	190	18	19	0	1	0	3	0	0	0	0	0	0	0
19. Finland	2	630	80	133	8	70	10	60	2	11	1	3	0	2	1
20. France	9	825	231	463	141	76	31	118	44	33	8	84	18	59	18
21. Georgia	2	32	15	0	0	0	0	0	0	0	0	0	0	0	0
22. Germany	12	1870	400	591	171	60	19	153	59	14	10	58	19	31	19

Country	Number of centres	MTX total	MTX new	ETN total	ETN new	INF total	INF new	ADA total	ADA new	ABA total	ABA new	ANA total	ANA new	Other total	Other new
23. Greece	3	312	53	95	32	0	0	55	24	0	0	2	2	0	0
24. Hungary	5	467	187	113	47	2	1	9	5	0	0	3	3	0	0
25. India	7	735	190	16	5	25	8	0	0	0	0	0	0	10	5
26. Iraq	1	4	3	0	0	0	0	0	0	0	0	0	0	0	0
27. Israel	6	249	56	81	25	14	4	31	16	9	4	6	1	5	2
28. Italy	25	1234	287	390	114	60	23	40	27	8	5	55	22	25	1234
29. Latvia	2	305	112	38	14	0	0	0	1	0	0	0	2	0	0
30. Libya	2	117	30	0	0	0	0	0	0	0	0	0	0	0	0
31. Lithuania	2	245	60	61	21	0	0	13	7	0	0	0	0	0	0
32. Mexico	8	660	99	100	21	18	5	33	10	9	0	0	0	1	1
33. Netherlands	7	906	266	261	83	17	6	41	16	1	1	57	22	13	7
34. New Zealand	1	130	12	60	8	0	0	5	1	0	0	3	0	5	1
35. Norway	3	370	48	123	29	55	13	26	10	4	1	20	4	13	5
36. Oman	1	35	5	14	4	3	3	0	0	0	0	0	0	0	0
37. Paraguay	1	41	20	0	0	0	0	6	3	0	0	0	0	0	0
38. Peru	3	952	182	14	8	4	1	2	2	10	0	0	0	0	0
39. Poland	7	720	185	192	34	0	0	7	7	0	0	0	0	0	0
40. Portugal	2	200	30	16	8	1	0	2	1	0	0	8	2	0	0
41. Romania	3	59	35	34	14	0	0	0	0	0	0	0	0	2	0
42. Russian Federation	3	1144	310	0	0	86	37	18	26	0	0	0	0	25	24
43. Saudi Arabia	4	185	40	98	30	15	8	24	12	0	0	6	6	5	6
44. Serbia	2	160	25	85	15	0	0	0	2	0	0	0	0	0	0
45. Slovakia	1	115	7	35	6	0	0	2	2	0	0	0	0	0	0
46. Slovenia	1	75	20	14	7	11	6	0	0	0	0	0	0	0	0
47. South Africa	2	275	45	2	2	3	1	4	3	0	0	0	0	0	0
48. Spain	8	1156	235	328	88	44	18	120	49	7	2	72	31	20	12
49. Sweden	4	406	71	124	28	15	5	36	16	3	3	7	2	5	5

Country	Number of centres	MTX total	MTX new	ETN total	ETN new	INF total	INF new	ADA total	ADA new	ABA total	ABA new	ANA total	ANA new	Other total	Other new
50. Switzerland	3	245	43	57	25	48	9	13	8	5	3	7	5	4	3
51. Turkey	5	421	131	132	49	25	12	5	2	1	1	15	14	2	2
52. United Arab Emirates	1	26	0	13	0	0	0	3	0	0	0	0	0	0	0
53. United Kingdom	7	1421	249	304	88	47	24	73	39	4	3	31	13	6	2
54. Venezuela	2	44	27	28	21	6	0	4	1	0	0	0	0	0	0
TOTAL	**205**	**21421**	**4858**	**5003**	**1490**	**925**	**320**	**1097**	**494**	**169**	**78**	**477**	**189**	**241**	**146**
TOTAL all biologics				**7912**	**2717**										

MTX: methotrexate; **ETN**: etanercept; **INF**: infliximab; **ADA**: adalimumab; **ABA**: abatacept; **ANA**: anakinra; **Other**: other biologic agents

Table 3: Time Oriented Table and Duration of Time for Each Specific Task

Months	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Personnel selection and training																				
Translation of material																				
Steering committee identification																				
Database, CRF and SOP development																				
Monitoring Staff including training																				
Submission to ethics committee																				
Contract agreement with centres																				
Investigator's meeting						x														
Dissemination and analysis																				
Patients enrolment																				
Regulatory documentation																				

Months	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Dissemination and analysis																				
Patients enrolment																				
Regulatory documentation																				

Months	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Dissemination and analysis																				
Patients enrolment																				
Regulatory documentation																				

REFERENCES

Bibliography

(1) Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007; 369(9563):767-78.

(2) Ruperto N, Levinson JE, Ravelli A, Shear ES, Tague BL, Murray K et al. Longterm health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. I. Outcome status. J Rheumatol 1997; 24(5):945-51.

(3) Ruperto N, Ravelli A, Levinson JE, Shear ES, Murray K, Tague BL et al. Longterm health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. II. Early predictors of outcome. J Rheumatol 1997; 24(5):952-8.

(4) Viola S, Felici E, Magni-Manzoni S, Pistorio A, Buoncompagni A, Ruperto N et al. Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. Arthritis Rheum 2005; 52(7):2092-102.

(5) Oliveira S, Ravelli A, Pistorio A, Castell E, Malattia C, Prieur AM et al. Proxy-reported health-related quality of life of patients with juvenile idiopathic arthritis: the Pediatric Rheumatology International Trials Organization multinational quality of life cohort study. Arthritis Rheum 2007; 57(1):35-43.

(6) Gutierrez-Suarez R, Pistorio A, Cespedes CA, Norambuena X, Flato B, Rumba I et al. Health-related quality of life of patients with juvenile idiopathic arthritis coming from 3 different geographic areas. The PRINTO multinational quality of life cohort study. Rheumatology 2007; 46(2):314-20.

(7) Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. N Engl J Med 1992; 326:1043-9.

(8) Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SKF, Falcini F et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum 2004; 50(7):2191-201.

(9) Ravelli A, Martini A. Methotrexate in juvenile idiopathic arthritis: answers and questions. J Rheumatol 2000; 27(8):1830-3.

(10) Lovell DJ, Giannini EH, Reiff A, Cawkwell D, Silverman ED, Nocton JJ et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 2000; 342(11):763-9.

(11) Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56(9):3096-106.

(12) Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008; 372(9636):383-91.

(13) Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 2008; 359(8):810-20.

(14) Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum 2010.

(15) Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis 2010; 69(4):718-22.

(16) Woo P, Southwood TR, Prieur AM, Doré CJ, Grainger J, David J et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000; 43(8):1849-57.

(17) Ruperto N, Ravelli A, Castell E, Gerloni V, Haefner R, Malattia C et al. Cyclosporine A in juvenile idiopathic arthritis. Results of the PRCSG/PRINTO phase IV post marketing surveillance study. Clin Exp Rheumatol 2006; 24(5):599-605.

(18) Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. N Engl J Med 2005; 352(16):1655-66.

(19) Van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, Ten Cate R, Suijlekom-Smit LW et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum 1998; 41(5):808-16.

(20) Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Juvenile rheumatoid arthritis in Rochester, Minnesota 1960-1993. Is the epidemiology changing? Arthritis Rheum 1996; 39:1385-90.

(21) Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P et al. Revision of the proposed classification criteria for juvenile idiopathic arthritides: Durban, 1997. J Rheumatol 1998; 25(10):1991-4.

(22) Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: Second revision, Edmonton, 2001. J Rheumatol 2004; 31(2):390-2.

(23) Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: Initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken) 2011; 63(4):465-82.

(24) Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997; 40(7):1202-9.

(25) Ruperto N, Ravelli A, Falcini F, Lepore L, De Sanctis R, Zulian F et al. Performance of the preliminary definition of improvement in juvenile chronic arthritis patients treated with methotrexate. Ann Rheum Dis 1998; 57(1):38-41.

(26) Albornoz MA. ACR formally adopts improvement criteria for juvenile arthritis (ACR Pediatric 30). ACR News 2002; 21(7):3.

(27) Magni-Manzoni S, Ruperto N, Pistorio A, Sala E, Solari N, Palmisani E et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum 2008; 59(8):1120-7.

(28) Wallace CA, Ruperto N, Giannini E, for The Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Pediatric Rheumatology International Trials Organization (PRINTO), and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004; 31(11):2290-4.

(29) Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum 2005; 52(11):3554-62.

(30) Ravelli A, Ioseliani M, Norambuena X, Sato J, Pistorio A, Rossi F et al. Adapted versions of the Sharp/van der Heijde score are reliable and valid for assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum 2007; 56(9):3087-95.

(31) Nielsen S, Ruperto N, Gerloni V, Simonini G, Cortis E, Lepore L et al. Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis. Clin Exp Rheumatol 2008; 26(4):688-92.

(32) Rossi F, Di DF, Galipo O, Pistorio A, Valle M, Magni-Manzoni S et al. Use of the sharp and larsen scoring methods in the assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum 2006; 55(5):717-23.

(33) Ravelli A, Viola S, Ramenghi B, Beluffi G, Zonta LA, Martini A. Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate. J Pediatr 1998; 133(2):262-5.

(34) Malattia C, Damasio MB, Magnaguagno F, Pistorio A, Valle M, Martinoli C et al. Magnetic resonance imaging, ultrasonography, and conventional radiography in the assessment of bone erosions in juvenile idiopathic arthritis. Arthritis Rheum 2008; 59(12):1764-72.

(35) Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol 2002; 29(5):1058-64.

(36) Cespedes-Cruz A, Gutierrez-Suarez R, Pistorio A, Ravelli A, Loy A, Murray KJ et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. Ann Rheum Dis 2008; 67(3):309-14.

(37) Ruperto N, Martini A. Pediatric rheumatology: JIA, treatment and possible risk of malignancies. Nat Rev Rheumatol 2011; 7(1):6-7.

(38) FDA. Early Communication About an Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, and Cimzia). http://www fda gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070725 htm [2008

(39) Diak P, Siegel J, La GL, Choi L, Lemery S, McMahon A. Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum 2010; 62(8):2517-24.

(40) Lehman TJ. Should the Food and Drug Administration warning of malignancy in children receiving tumor necrosis factor alpha blockers change the way we treat children with juvenile idiopathic arthritis? Arthritis Rheum 2010; 62(8):2183-4.

(41) Simard J, Neovius M, Hagelberg S, Askling J. Juvenile idiopathic arthritis and risk of cancer: A nationwide cohort study. Arthritis Rheum 2010.

(42) Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, Ruperto N et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005; 146(5):598-604.

(43) Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009; 61(5):658-66.

(44) Zink A, Askling J, Dixon WG, Klareskog L, Silman AJ, Symmons DP. European biologicals registers: methodology, selected results and perspectives. Ann Rheum Dis 2009; 68(8):1240-6.

(45) Kremer JM, Greenberg J. Interpreting registry-derived drug studies: Does societal context matter? Arthritis Rheum 2009; 60(11):3155-7.

(46) Simon LS, Strand CV, Boers M, Brooks PM, Tugwell PS, Bombardier C et al. How to ascertain drug safety in the context of benefit. Controversies and concerns. J Rheumatol 2009; 36(9):2114-21.

(47) Simon LS, Strand CV, Boers M, Brooks PM, Henry D, Tugwell PS. Observations from the OMERACT Drug Safety Summit, May 2008. J Rheumatol 2009; 36(9):2110-3.

(48) FDA. FDA Media Teleconference on TNF Inhibitors. Tumor Necrosis factor-á blockers . http://www fda gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM169323 pdf [2008 :[1-21]

(49) FDA. FDA: Cancer Warnings Required for TNF Blockers. http://www fda gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803 htm [2009

(50) Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C et al. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis 2009; 68(5):648-53.

(51) Askling J, van Vollenhoven RF, Granath F, Raaschou P, Fored CM, Baecklund E et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: Does the risk change with the time since start of treatment? Arthritis Rheum 2009; 60(11):3180-9.

(52) Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis 2009; 68(7):1177-83.

(53) Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies:

systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006; 295(19):2275-85.

(54) Pincus T, Sokka T. Quantitative clinical rheumatology: "keep it simple, stupid": MDHAQ function, pain, global, and RAPID3 quantitative scores to improve and document the quality of rheumatologic care. J Rheumatol 2009; 36(6):1099-100.

(55) Filocamo G, Consolaro A, Schiappapietra B, Dalprà S, Lattanzi B, Magni-Manzoni S et al. Introducing a new approach into clinical care of children with juvenile idiopathic arthritis: the Juvenile Arthritis Multidimensional Assessment Report. J Rheumatol 2011; in press.

(56) Filocamo G, Sztajnbok F, Cespedes-Cruz A, Magni-Manzoni S, Pistorio A, Viola S et al. Development and validation of a new short and simple measure of physical function for juvenile idiopathic arthritis. Arthritis Rheum 2007; 57(6):913-20.

(57) Filocamo G, Schiappapietra B, Bertamino M, Pistorio A, Ruperto N, Magni-Manzoni S et al. A new short and simple health-related quality of life measure for paediatric rheumatic diseases: initial validation in juvenile idiopathic arthritis. Rheumatology 2010; Epub ahead of print.

(58) Eberhard BA, Sison MC, Gottlieb BS, Ilowite NT. Comparison of the Intraarticular effectiveness of triamcinolone hexacetonide and triamcinolone acetonide in treatment of juvenile rheumatoid arthritis. J Rheumatol 2004; 31(12):2507-12.

(59) Uziel Y, Berkovitch M, Gazarian M, Koren G, Silverman ED, Schneider R et al. Evaluation of eutectic lidocaine/prilocaine cream (EMLA$^{(R)}$) for steroid joint injection in children with juvenile rheumatoid arthritis: A double blind, randomized, placebo controlled trial. J Rheumatol 2003; 30(3):594-6.

(60) Zulian F, Martini G, Gobber D, Plebani M, Zacchello F, Manners P. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology 2004; 43(10):1288-91.

(61) Zulian F, Martini G, Gobber D, Agosto C, Gigante C, Zacchello F. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. Rheumatology 2003; 42(10):1254-9.

(62) Padeh S, Passwell JH. Intraarticular corticosteroid injection in the management of children with chronic arthritis. Arthritis Rheum 1998; 41(7):1210-4.

(63) Huppertz HI, Tschammler A, Horwitz AE, Schwab KO. Intraarticular corticosteroids for chronic arthritis in children: efficacy and effects on cartilage and growth. J Pediatr 1995; 127(2):317-21.

(64) Menninger H, Reinhardt S, Sondgen W. Intra-articular treatment of rheumatoid knee-joint effusion with triamcinolone hexacetonide versus sodium morrhuate. A prospective study. Scand J Rheumatol 1994; 23(5):249-54.

(65) Moher D, Schulz KF, Altman DG, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357(9263):1191-4.

(66) Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG et al. CONSORT for reporting randomised trials in journal and conference abstracts. Lancet 2008; 371(9609):281-3.

(67) Gray RJ. Estimation of regression parameters and the hazard function in transformed linear survival models. Biometrics 2000; 56(2):571-6.

(68) Gray RJ. Some diagnostic methods for Cox regression models through hazard smoothing. Biometrics 1990; 46(1):93-102.

(69) Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum 2009; 60(9):2794-804.

(70) Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Stat Med 1982; 1(2):121-9.

(71) Cassidy JT, Levinson JE, Bass JC, Baum J, Brewer EJ, Fink CW et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. Arthritis Rheum 1986; 29:274-81.

(72) Bazso A, Consolaro A, Ruperto N, Pistorio A, Viola S, Magni-Manzoni S et al. Development and testing of reduced joint counts in juvenile idiopathic arthritis. J Rheumatol 2009; 36(1):183-90.

(73) Ruperto N, Giannini EH. Redundancy of conventional articular response variables used in juvenile chronic arthritis clinical trials. Ann Rheum Dis 1996; 55:73-5.

(74) Ravelli A, Viola S, Ruperto N, Corsi B, Ballardini G, Martini A. Correlation between conventional disease activity measures in juvenile chronic arthritis. Ann Rheum Dis 1997; 56(3):197-200.

(75) Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994; 37:1761-9.

(76) Guest Editors, Martini A, Ruperto N, for the Paediatric Rheumatology International Trials Organization (PRINTO). Quality of life in juvenile idiopathic arthritis patients compared to healthy children. Clin Exp Rheumatol 2001; 19 (suppl. 23):S1-S172.

(77) Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L et al. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol 2001; 19(4):S1-S9.

(78) Bazso A, Consolaro A, Ruperto N, Pistorio A, Viola S, Magni-Manzoni S et al. Development and Testing of Reduced Joint Counts in Juvenile Idiopathic Arthritis. J Rheumatol 2008.